12° Πανελλήνιο Συνέδριο
ΕΠΕΜΥ
Επιστημονική Εταιρεία για τη Μυοσκελετική Υγεία
Ολοκληρωμένη διαχείριση των Φλεγμονωδών και των Μυοσκελετικών Παθήσεων
29 Οκτωβρίου - 01 Νοεμβρίου 2020
Ξενοδοχείο Valis
Βόλος

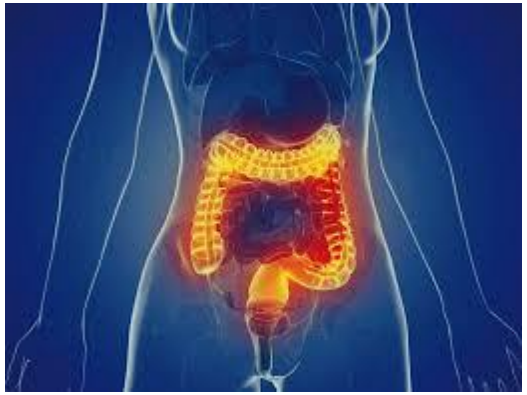
Άντι-ρευματικά φάρμακα και επιδράσεις τους σε ασθενείς με ΙΦΝΕ

Δημήτρης Τσερώνης
Ρευματολόγος
Επιστημονικός Συνεργάτης
Δ ππκ ,ΠΓΝ «Αττικόν»

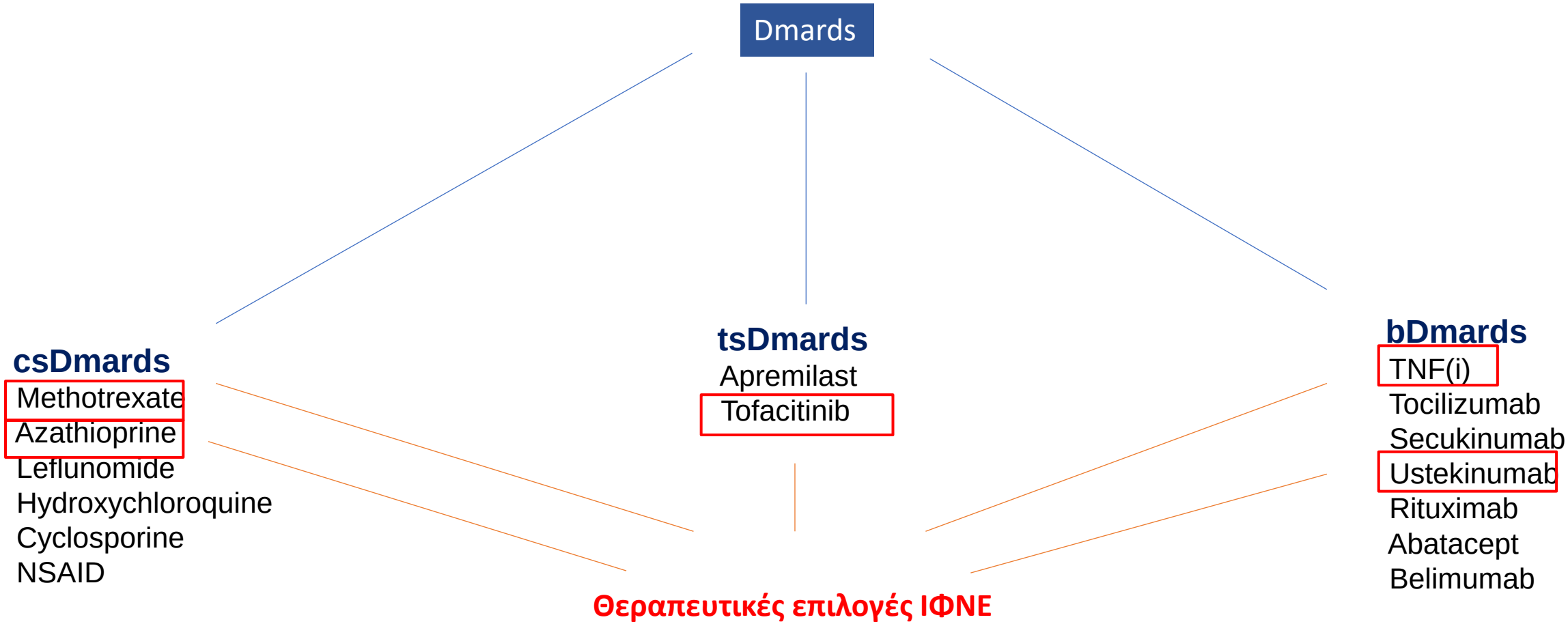

return
shift
Conflict of Interest
YES
NO

περίγραμμα ομιλίας

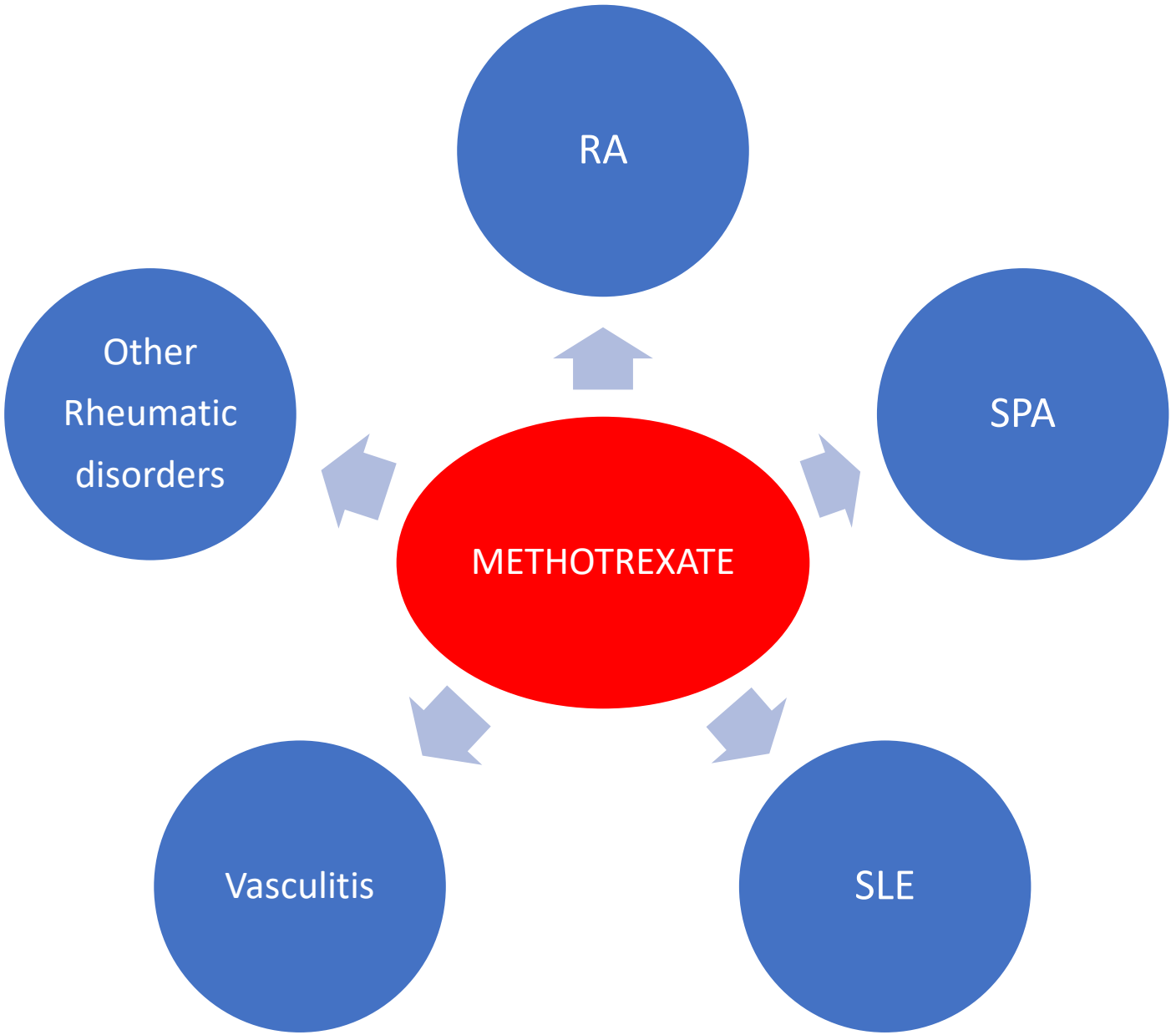
- Τα φάρμακα στις Ρευματικές παθήσεις
- csDmards …..*The usual suspects*
- NSAID … *the other point of view*
- TNF- inhibitors…. *Friends or foe*
- Anti –IL-17 inhibitors , anti-IL-12/23 inhibitors…. *True or false*
- tsDmards… *the new kid on the block*



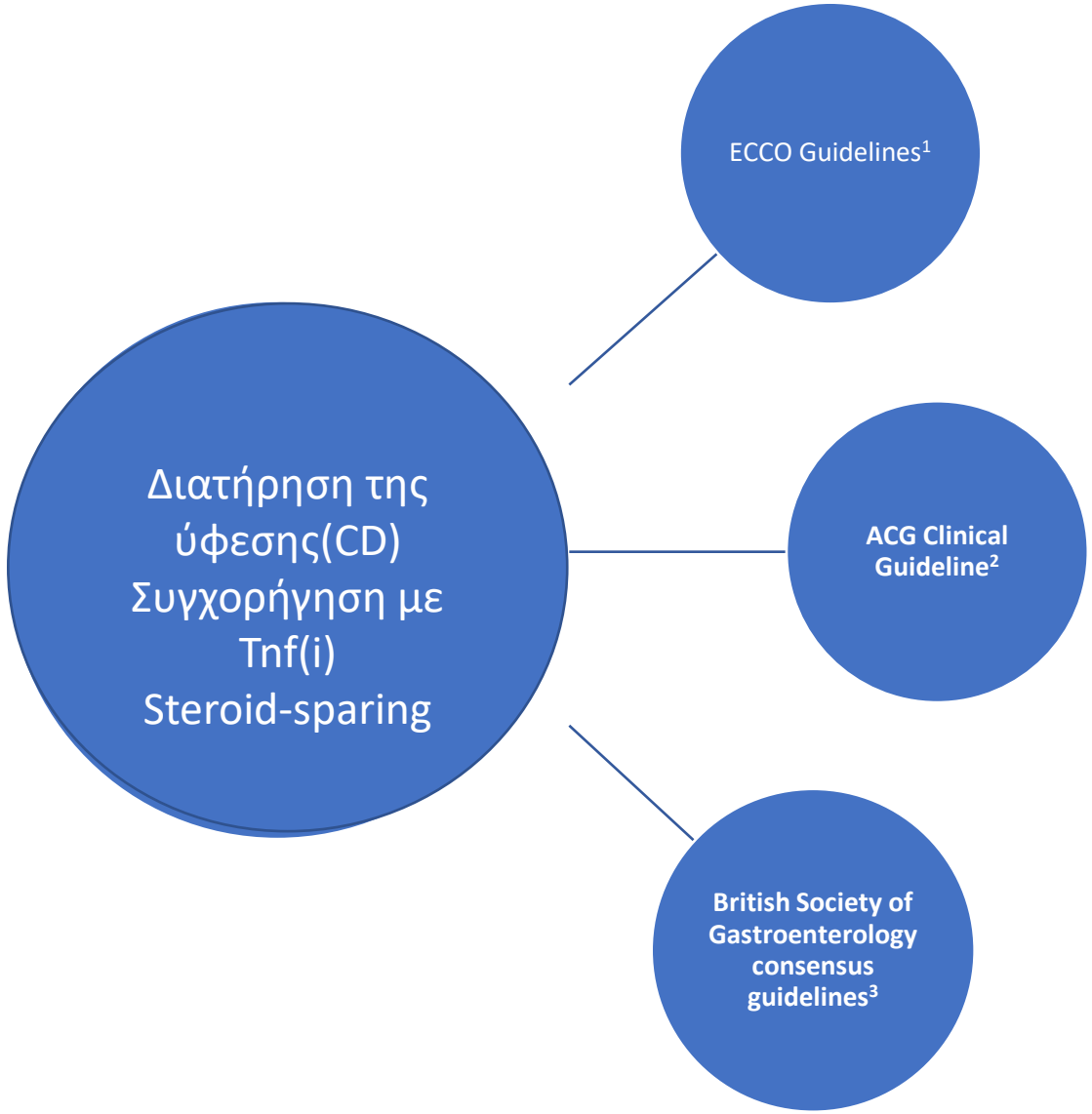
Τα Αντι-ρευματικά Φάρμακα



Η Μεθοτρεξάτη στις Ρευματικές παθήσεις



Η Μεθοτρεξάτη στις ΙΦΝΕ… Guidelines



Methotrexate

Recommendation 2.4. ECCO CD Treatment GL [2019]

We recommend methotrexate administered parenterally for the maintenance of remission in patients with steroid-dependent Crohn's disease [weak recommendation, moderate-quality evidence].

"Methotrexate (up to 25 mg once weekly IM or SC) is effective and should be considered for use in alleviating signs and symptoms in patients with steroid-dependent Crohn's disease and for maintaining remission ([199,200]) *(conditional recommendation, low level of evidence).*

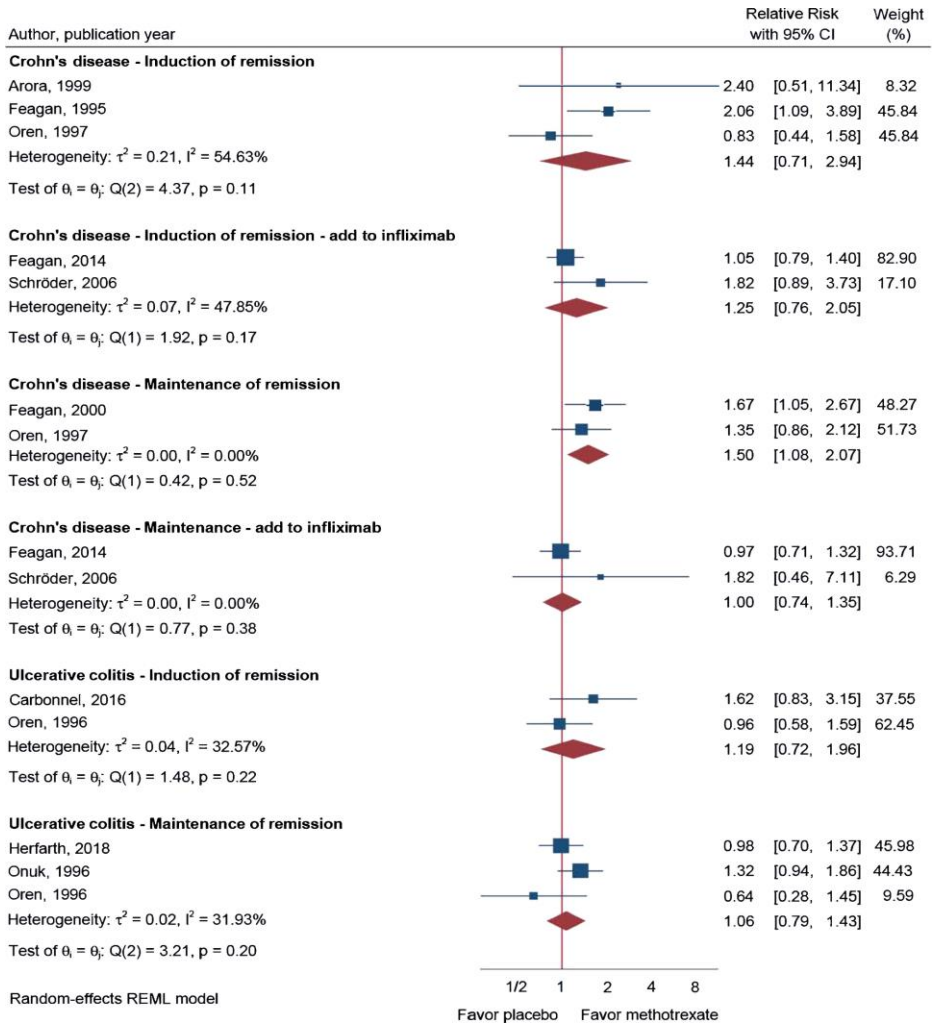
4.4.1.2 Methotrexate

Statement 41. We suggest that methotrexate may be used for the maintenance of remission of Crohn's disease, and the dose should be at least 15 mg weekly. Subcutaneous administration has better bioavailability than oral, particularly at higher doses (GRADE: weak recommendation, moderate-quality evidence. Agreement: 88.4%).

1,ECCO Guidelines on Therapeutics in Crohn's Disease: Medical Treatment, *Journal of Crohn's and Colitis*, Volume 14, Issue 1, January 2020,
2.ACG Clinical Guideline: Management of Crohn's Disease in Adults, American Journal of Gastroenterology: April 2018
3.,British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adultsGut 2019;68:s1-s106.

Η Μεθοτρεξάτη στις ΙΦΝΕ

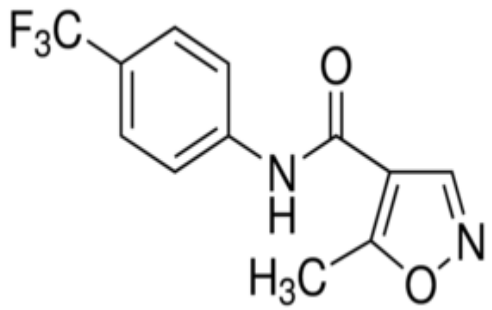
Efficacy and safety of methotrexate in the management of inflammatory bowel disease: A systematic review and meta-analysis of randomized ,controlled trials



- MTX monotherapy **was not superior** to placebo for induction of clinical remission in Crohn's disease(CD)
- MTX **was superior** to placebo in maintaining clinical remission of CD
- MTX **is not confirmed** to be effective for treatment of UC
- Concomitant therapy with MTX and the TNF inhibitor infliximab (IFX) **was not superior** to IFX monotherapy in CD.
- CD studies showed a significantly **higher risk of AEs when comparing MTX versus placebo** in studies investigating induction of remission, but not in maintenance of remission.

EClinicalMedicine 2020 20DOI: (10.1016/j.eclinm.2020.100271)

Η Λεφλουνομίδη στις ΙΦΝΕ



- Βελτίωση της αρθρίτιδας
- Μείωση της κορτιζόνης
- ηλικιωμένοι

- «λίγα» δεδομένα
- όχι RCT- trials
- ↑ ανεπιθύμιτες ενέργειες

Dig Dis Sci. 2008 Apr;53(4):1025-32

J Clin Gastroenterol. 2003 Aug;37(2):125-8

Η Υδροξυχλωροκίνη στις ΙΦΝΕ

OC-140 Hydroxychloroquine as a treatment for crohn's disease: enhancing antibiotic efficacy and macrophage killing of E coli

Conclusion : Hydroxychloroquine enhances antibiotic efficacy and macrophage killing of AIEC. Its mechanism of action is not via pH dependent iron metabolism but is likely due to direct phagolysosomal pH changes. Further work is required to determine its mechanism of action but it holds potential as a treatment for Crohn's.

Gut 2012;61:A60-A61

«Ασφαλής» θεραπευτική επιλογή σε ήπιες εντεροπαθητικές αρθρίτιδες

Randomized Trial of Ciprofloxacin Doxycycline and Hydroxychloroquine Versus Budesonide in Active Crohn’s Disease

Conclusion : Overall results with this antibiotic/hydroxychloroquine combination were unimpressive, but long-term remission is seen in some patients and justifies further study.

Randomized Trial of Ciprofloxacin Doxycycline and Hydroxychloroquine Versus Budesonide in Active Crohn’s Disease. *Dig Dis Sci* (2020)

Η Αζαθειοπρίνη στις ΙΦΝΕ

Θεραπεία σε μη σοβαρές κορτικο-εξαρτώμενες ΙΦΝΕ[1]

Διατήρηση της ύφεσης σε CD/UC[2]

Συγχόρηγηση με TNF(i)[3] και σε αλλαγή σε 2 TNF(i)[4]

1.Louis, E., Irving, P., & Beaugerie, L. (2014). *Use of azathioprine in IBD: modern aspects of an old drug.*

2.European Journal of Public Health, Volume 30, Issue Supplement_5, September 2020,

3.Appropriateness of combinationtherapy for patients with inflammatory bowel diseases: one size still does not fit all.Clin Gastroenterol Hepatol. 2018

4.Papamichael, K., Cheifetz, A. S., & Irving, P. M. (2020). *New role for azathioprine in case of switching anti-TNFs in IBD. Gut,*

ΜΣΑΦ και ΙΦΝΕ

Aspirin, nonsteroidal anti-inflammatory drug use, and risk for Crohn disease and ulcerative colitis: a cohort study

Variable	0 tablets/wk	0.5–1.5 tablets/wk	2–5 tablets/wk	>5 tablets/wk
NSAIDs				
Person-years of follow-up	600 068	314 140	198 903	182 207
CD				
Cases, *n*	48	25	24	26
Age-adjusted incidence, *n*†	8	8	12	14‡
Age-adjusted HR (95% CI)	1.00 (reference)	1.13 (0.69–1.86)	1.72 (1.04–2.84)	1.78 (1.10–2.89)
Multivariate HR (95% CI)§	1.00 (reference)	1.09 (0.66–1.80)	1.68 (1.02–2.78)	1.71 (1.05–2.77)
UC				
Cases, *n*	47	23	20	27
Age-adjusted incidence, *n*†	8	7	10	15‡
Age-adjusted HR (95% CI)	1.00 (reference)	1.03 (0.62–1.71)	1.38 (0.81–2.36)	1.90 (1.18–3.07)
Multivariate HR (95% CI)§	1.00 (reference)	1.00 (0.60–1.66)	1.30 (0.76–2.21)	1.78 (1.10–2.89)

«δοσο-εξαρτημένη» επίπτωση ΙΦΝΕ

Conclusion

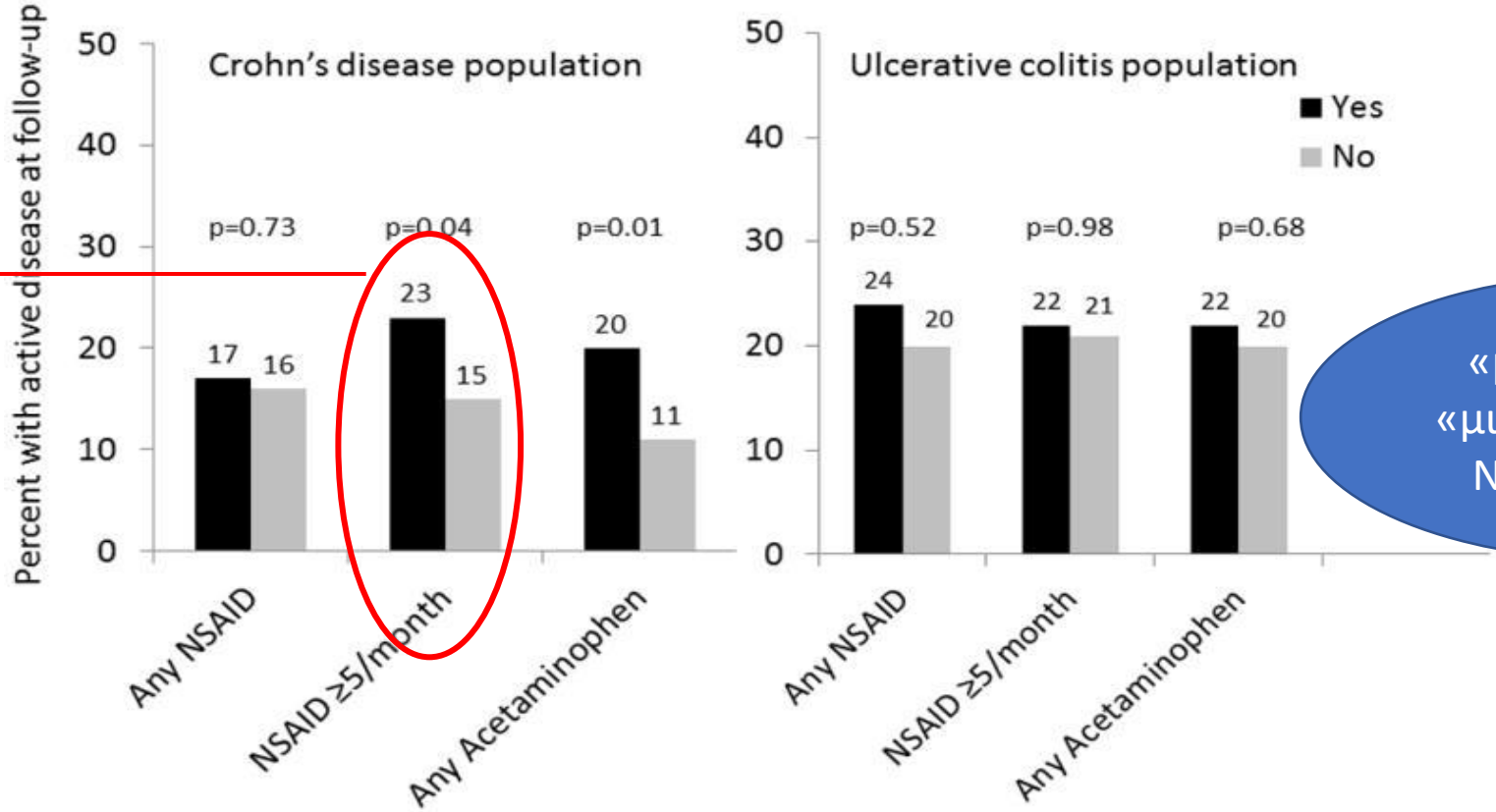
Frequent use of NSAIDs but not aspirin seemed to be associated with increased absolute incidence of CD and UC.

Aspirin, nonsteroidal anti-inflammatory drug use, and risk for Crohn disease and ulcerative colitis: a cohort study. *Ann Intern Med*. 2012;156(5):350-359.

ΜΣΑΦ και ΙΦΝΕ

Role of Non-Steroidal Anti-Inflammatory Drugs in Exacerbations of Inflammatory Bowel Disease

Υψηλή ενεργότητα σε αυξημένη λήψη ΜΣΑΦ



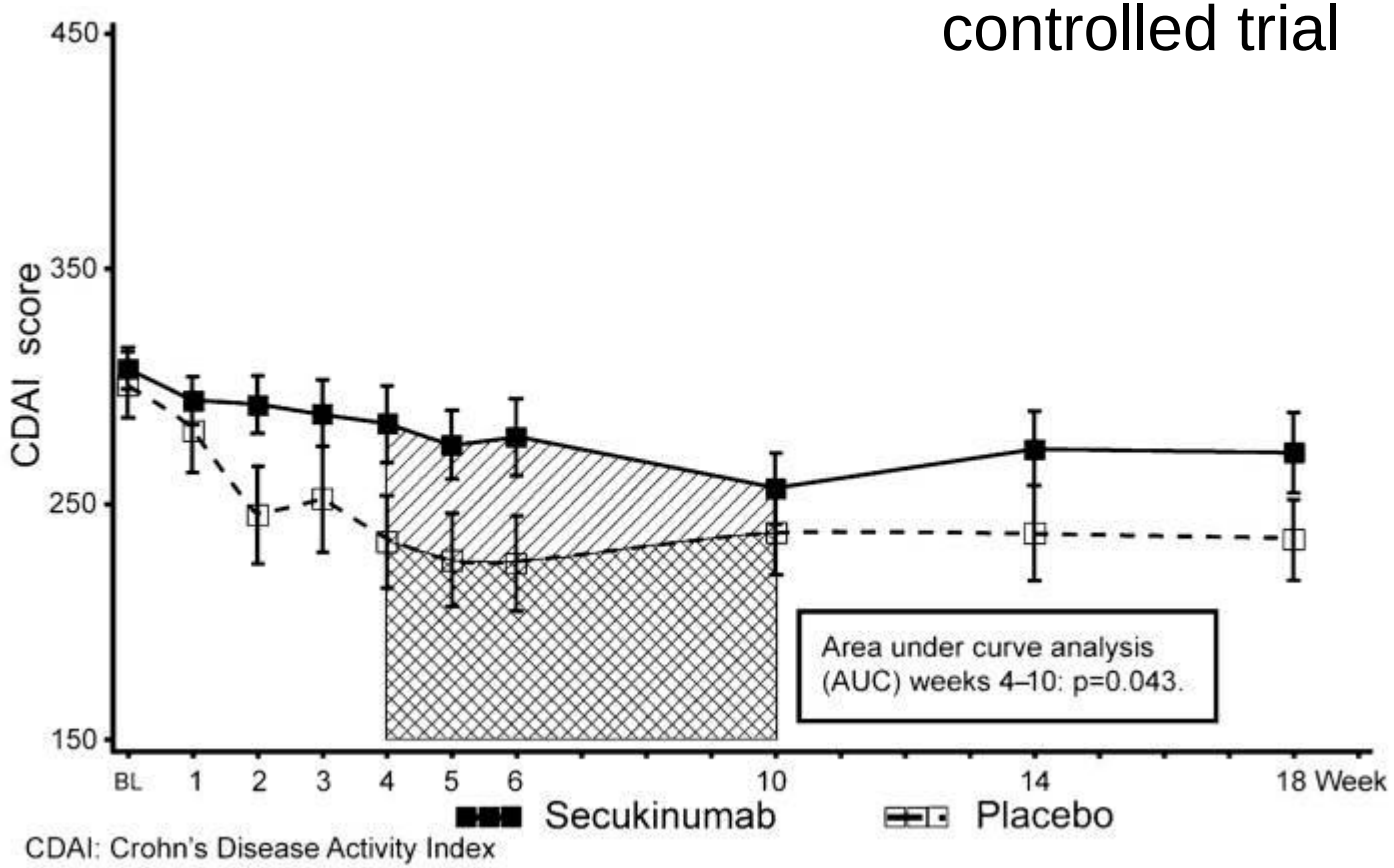
«μικρές» δόσεις
«μικρής» διάρκειας
Νεότερα ΜΣΑΦ

CONCLUSIONS

Regular (≥ 5 times/monthly) NSAID and acetaminophen **use were associated with active CD**, but not UC. Less frequent NSAID use was not associated with active CD or UC.

Η καταστολή της IL-17 στις ΙΦΝΕ

Secukinumab, a human anti-IL-17A monoclonal antibody, for moderate to severe Crohn's disease: unexpected results of a randomised, double-blind placebo-controlled trial



■ secukinumab

□ placebo

«Αναποτελεσματικό» στις ΙΦΝΕ - **αυξημένη** επίπτωση λοιμώξεων

Gut. 2012 Dec; 61(12): 1693–1700.

Η καταστολή της IL-17 στις ΙΦΝΕ

Incidence rates of inflammatory bowel disease in patients with psoriasis, psoriatic arthritis and ankylosing spondylitis treated with secukinumab: a retrospective analysis of pooled data from 21 clinical trials

Table 2 EAIRs (95% CI) of IBD over the entire treatment period for patients taking any dose of secukinumab

	PsO Studies N=5181	PsA Studies N=1380	AS Studies N=794
Median exposure (min–max), days	505.0 (1–1825)	1067.5 (8–1827)	981.5 (1–1530)
Total exposure, PY	10 416.9	3866.9	1943.1
Incidence, identified by standard definition (preferred term)			
CD, EAIR per 100 PY (95% CI)	0.05 (0.02 to 0.11)	0.08 (0.02 to 0.23)	0.4 (0.2 to 0.8)
UC, EAIR per 100 PY (95% CI)	0.13 (0.07 to 0.23)	0.08 (0.02 to 0.23)	0.2 (0.1 to 0.5)
IBDU, EAIR per 100 PY (95% CI)	0.01 (0.00 to 0.05)	0.05 (0.01 to 0.19)	0.1 (0.0 to 0.3)

EAIR data are displayed to two decimals where N>1000; if N<1000, then data are displayed to one decimal.
AS, ankylosing spondylitis; CD, Crohn's disease; EAIR, exposure-adjusted incidence rate; IBD, inflammatory bowel disease; IBDU, IBD-unclassified; PY, patient-years; PsA, psoriatic arthritis; PsO, psoriasis; UC, ulcerative colitis.

n=**7355**

41 περιπτώσεις ΙΦΝΕ
-**30** new- onset
-**11** έξαρση

«Χαμηλή» επίπτωση ΙΦΝΕ - **0,56%** των συνολικών περιπτώσεων

Ann Rheum Dis2019;78:473–479.

Η καταστολή της IL-17 στις ΙΦΝΕ

Paradoxical gastrointestinal effects of interleukin-17 blockers

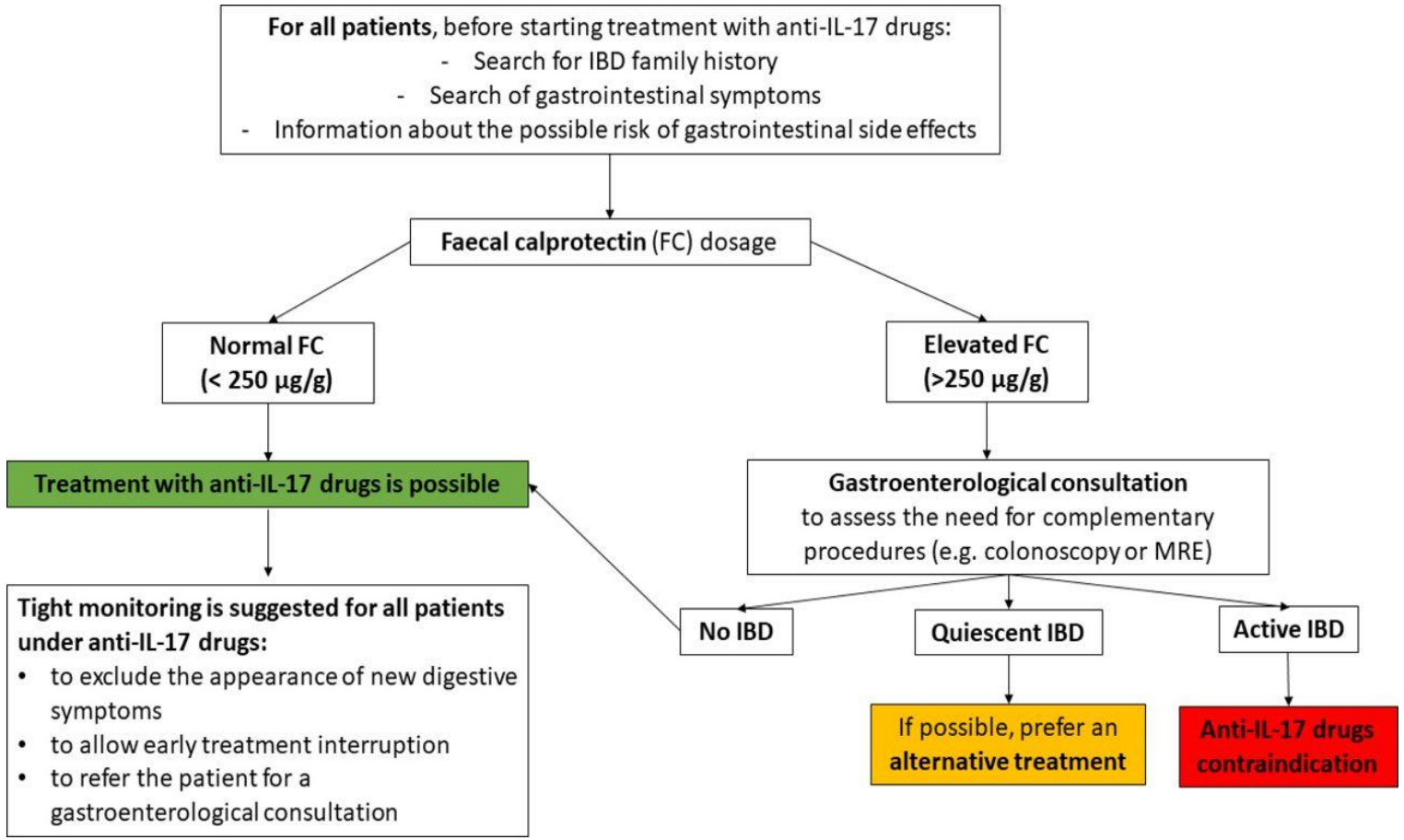
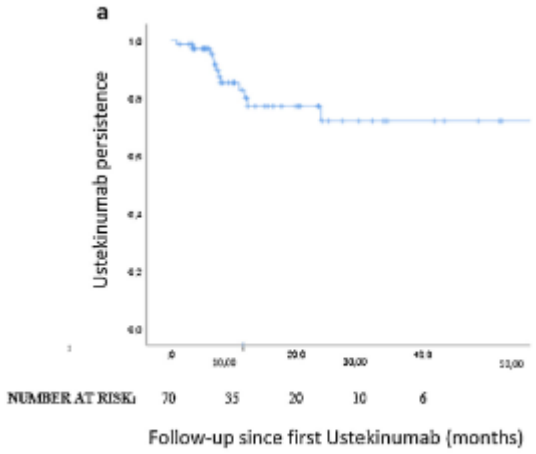


Figure 4 Practical recommendations before anti-IL-17 drug initiation recommendations are based on the experience of the authors

Marine Fauny et al. Ann Rheum Dis 2020;79:1132-1138

Η καταστολή της IL-12/23 στις ΙΦΝΕ

Real-life effectiveness of ustekinumab in inflammatory bowel disease patients with concomitant psoriasis or psoriatic arthritis: An IG-IBD study



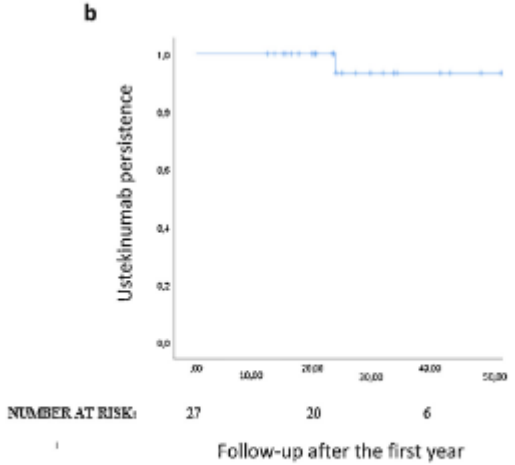


Fig. 1. (a, b) Kaplan–Meier survival curves for ustekinumab persistence. (a) For 70 IBD patients. (b) For the subgroup of 27 patients with long-term remission.

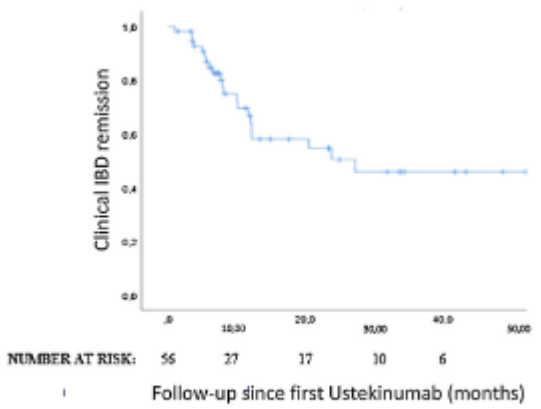


Fig. 2. Kaplan–Meier survival curve for clinical IBD remission among 56 (80%) of 70 patients with clinically active disease at baseline.

Ανταπόκριση στις ΙΦΝΕ και σε χαμηλότερες δόσεις ?

Dig Liver Dis. 2019 Jul;51(7):972-977

TNF- inhibitors

Ρευματικές παθήσεις

Infliximab

Adalinumab

Golinumab

Etanercept

Certolizumab pegol

ΙΦΝΕ

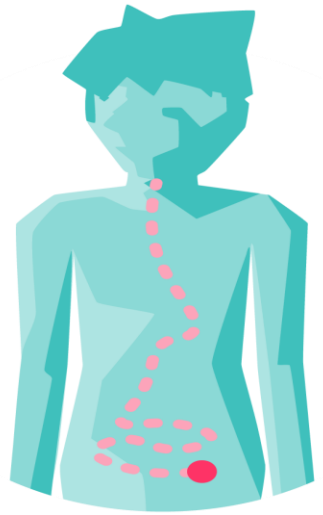
Infliximab

Adalinumab

Golinumab

Certolizumab pegol

(USA)



Η Ετανερσεπτη στις ΙΦΝΕ

Etanercept for active Crohn's disease: A randomized, double-blind, placebo-controlled trial

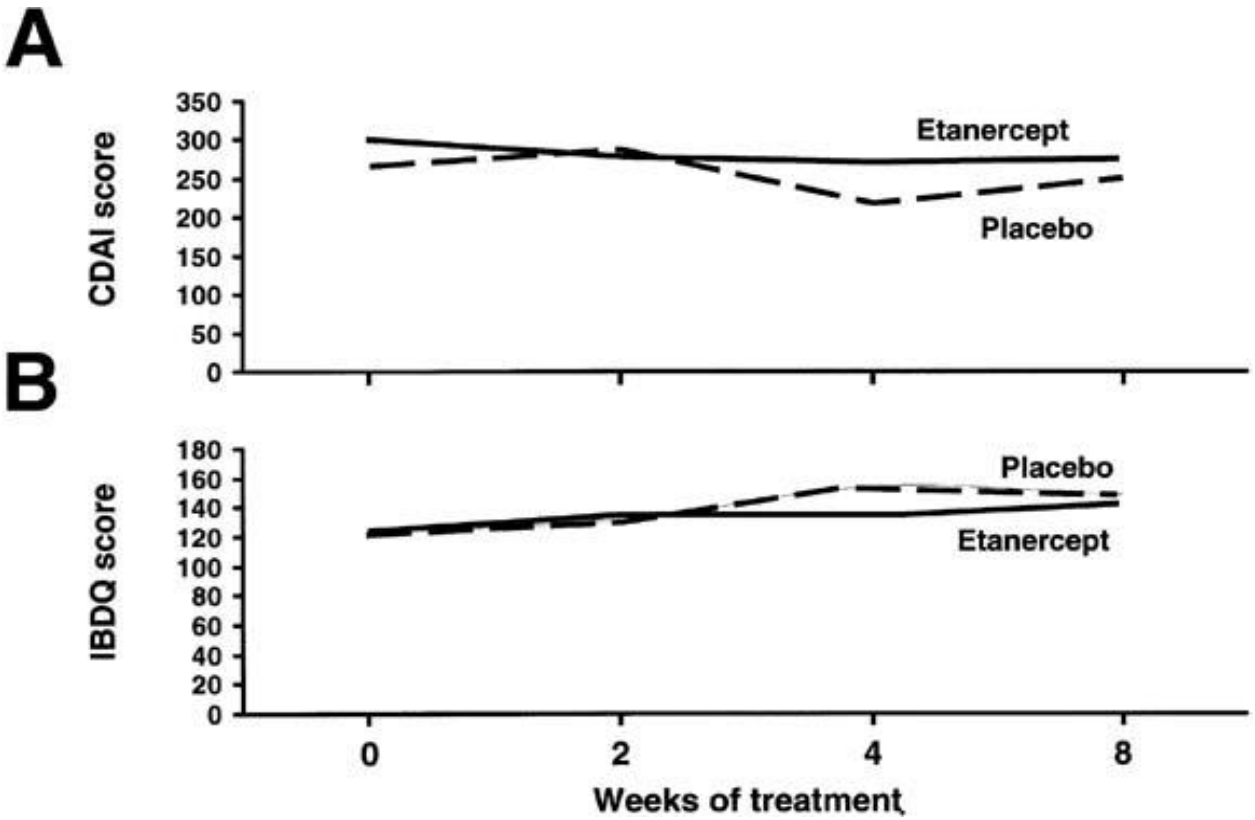


Fig. 2Median scores at each study visit, according to treatment group. None of the differences **were statistically significant**. (*A*) CDAI; (*B*) IBDQ quality of life index.

Ασφαλές, αλλά όχι αποτελεσματικό!

Conclusions: Subcutaneous etanercept at a dose of 25 mg twice weekly is safe, but not effective, for the treatment of patients with moderate to severe Crohn's disease.

Etanercept for active Crohn's disease: a randomized, double-blind, placebo-controlled trial. Gastroenterology. 2001 Nov;121(5):1088-94.

Η Ετανερσέπτη στις ΙΦΝΕ… «παράδοξη» κολίτιδα

Antitumor Necrosis Factor-α Therapy Associated with Inflammatory Bowel Disease: Three Cases and a Systematic Literature Review

- **56** περιπτώσεις επαγόμενης ΙΦΝΕ από ετανερσέπτη
- Οι περισσότεροι ασθενείς **38/56** εμφάνισαν **νόσο Crohn**
- Η εντεροπάθεια εμφανίστηκε περίπου **27 μήνες** μετά την χορήγηση ετανερσέπτης
- Στους περισσότερους ασθενείς τα συμπτώματα **βελτιώθηκαν μετά την διακοπή** της εταναρσέπτης

The Journal of Rheumatology April 2017, jrheum.160952

η Ετανερσέπτη στις ΙΦΝΕ… «παράδοξη» κολίτιδα

Increased risk of developing Crohn's disease or ulcerative colitis in 17 018 patients while under treatment with anti-TNFα agents, particularly etanercept, for autoimmune diseases other than inflammatory bowel disease

TABLE 2
Hazard ratio (HR) of de novo **Crohn's disease** following use of anti-TNFα prescribed for autoimmune diseases, multivariate Cox proportional hazard model and adjusted estimates with confidence interval

	N outcome	Median time at risk (mo)	Model 1[a] HR (95 CI)	Model 2[b] HR (95 CI)
Exposure to TNF-alpha				
Infliximab	17	13	1.4 (0.8-2.2)	1.3 (0.8-2.2)
Etanercept	31	15	1.9 (1.4-2.9)	2.0 (1.4-2.8)
Adalimumab	24	20	1.2 (0.8-1.8)	1.2 (0.8-1.8)
Golimumab	9	14	2.1 (1.1-4.0)	2.0 (1.0-3.9)
Certolizumab pegol	6	9	2.1 (1.0-4.8)	2.2 (1.0-4.9)
Non-exposed	337	90	1	

[a]Adjustments are made for type of underlying autoimmune disease.
[b]Adjustments are made for gender, age at first autoimmune disease and type of underlying autoimmune disease.

TABLE 3
Hazard ratio (HR) of de novo **UC** following use of anti-TNFα prescribedfor autoimmune diseases, multivariate Cox proportional hazard model and adjusted estimates with 95 confidence interval

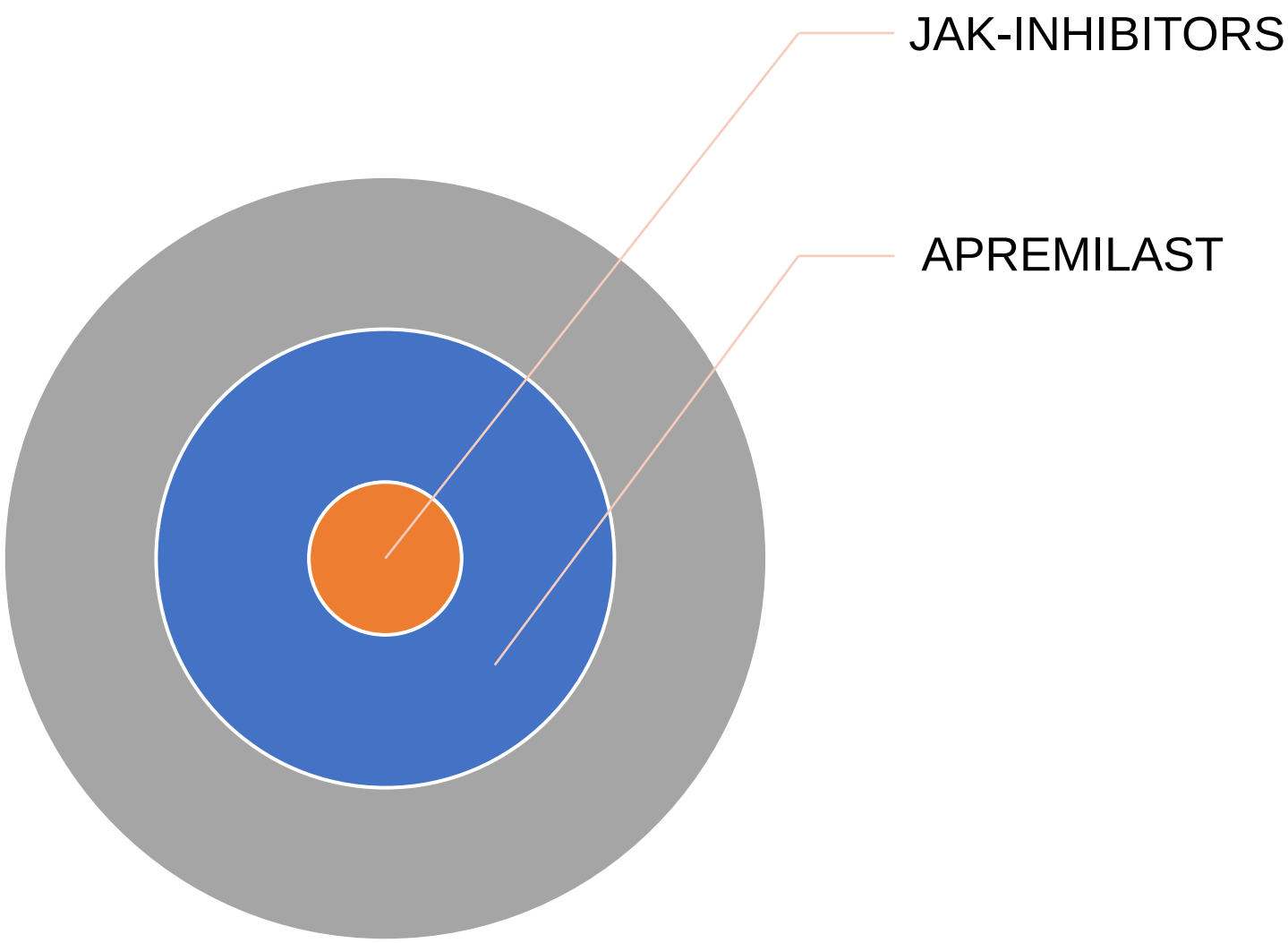
	N outcome	Median time at risk (mo)	Model 1 HR[a] (95 CI)	Model 2[b] HR (95 CI)
Exposure to TNF-alpha				
Infliximab	16	13	1.0 (0.6-1.6)	1.0 (0.6-1.6)
Etanercept	40	14	2.0 (1.5-2.8)	2.0 (1.5-2.8)
Adalimumab	14	20	0.6 (0.3-1.0)	0.6 (0.3-1.0)
Golimumab	4	12	1.0 (0.4-2.6)	1.0 (0.4-2.6)
Certolizumab pegol	4	9	1.3 (0.5-3.5)	1.3 (0.5-3.4)
Non-exposed	541	89	1	1

[a]Adjustments are made for type of underlying autoimmune disease.
[b]Adjustments are made for gender, age at first autoimmune disease and type of underlying autoimmune disease.

Αυξημένος κίνδυνός επίπτωσης ΙΦΝΕ σε ασθενής που λαμβάνουν ΕΤΝ

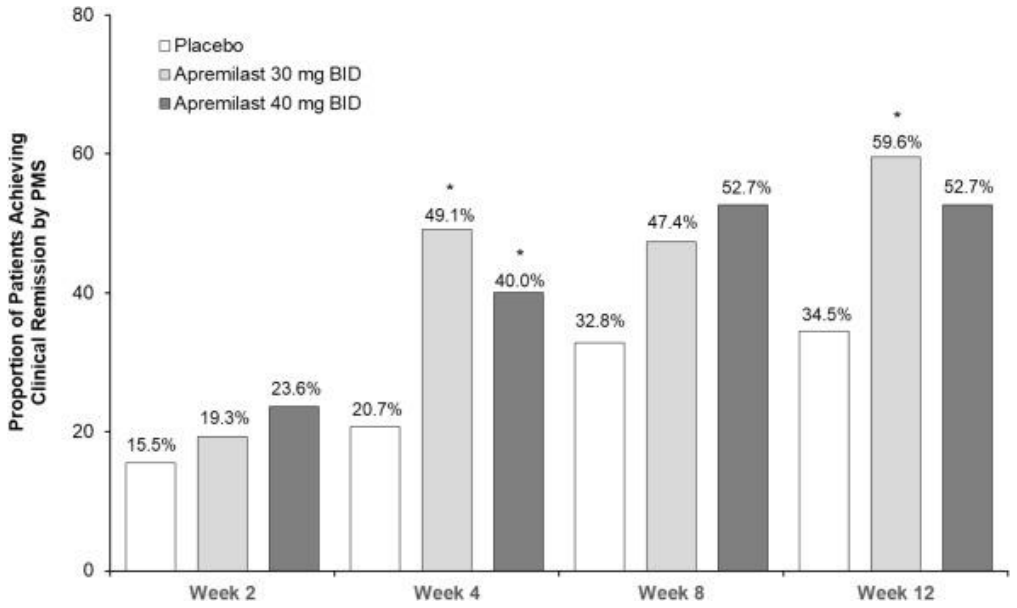
Aliment Pharmacol Ther. 2019 Aug;

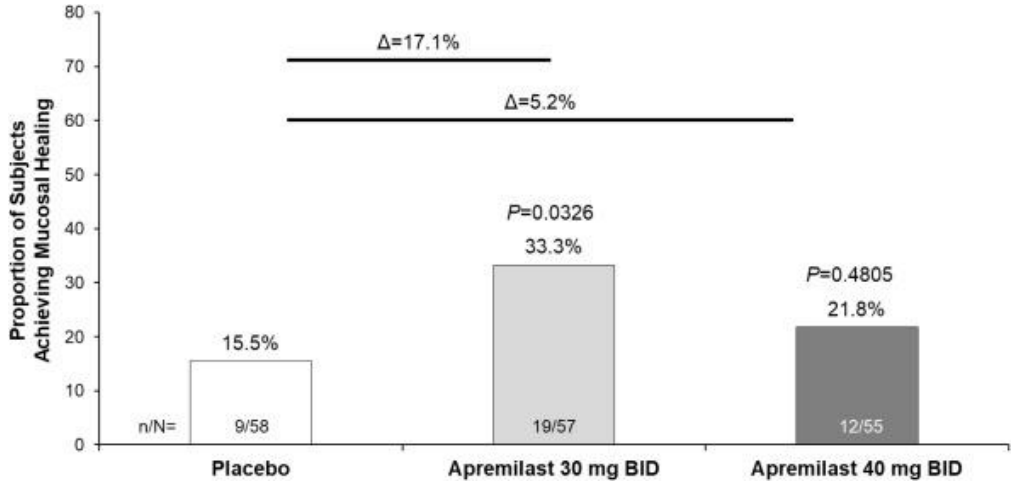
tsDmards… ενδοκυττάριος θεραπευτικός «Στόχος»



Η Απρεμιλάστη στην Ελκώδη κολίτιδα

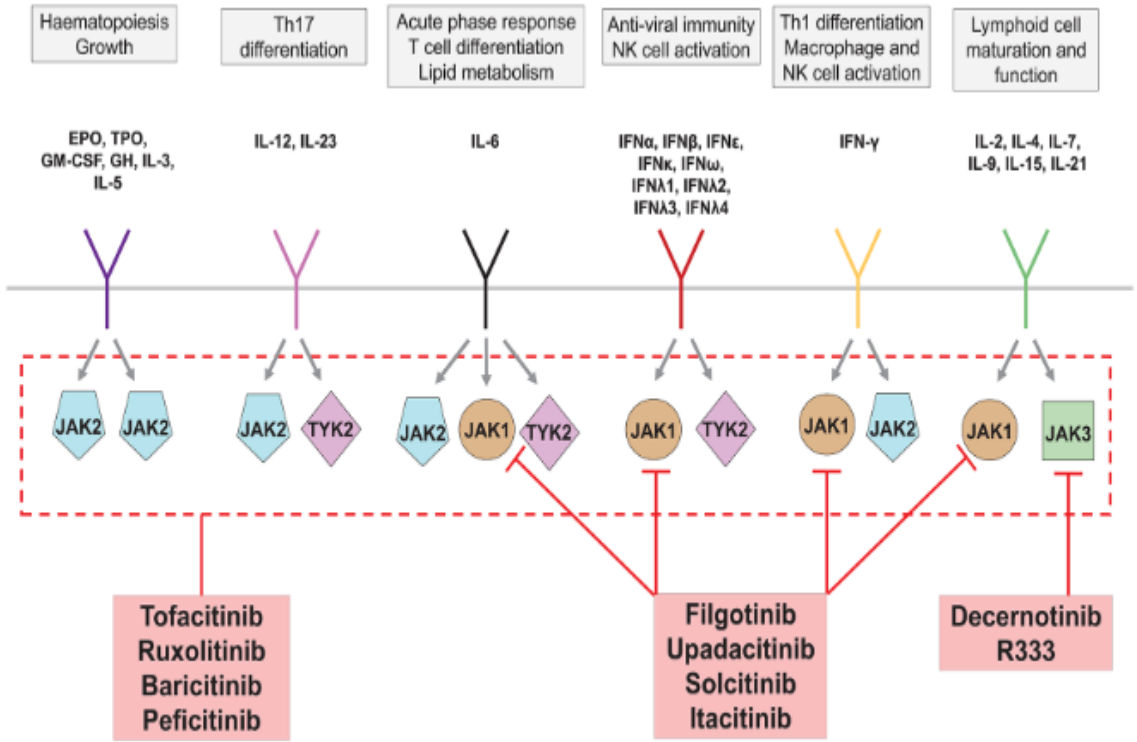
Effects of Apremilast, an Oral Inhibitor of Phosphodiesterase 4, in a Randomized Trial of Patients With Active Ulcerative Colitis





Βελτίωση αλλά **όχι** επίτευξη του primary endpoint
Καλό προφίλ ασφάλειας (συχνότερη ανεπιθύμητη-**κεφαλαλγία ;**)

Η αναστολή του μονοπατιού - JAK στις ΙΦΝΕ



Drug	Mode of delivery	Clinical efficacy demonstrated	Approval state[a]	Ref
JAK inhibitors				
Tofacitinib	JAK1/JAK3	For UC, in CD primary end point of a phase IIb study was missed	For UC, rheumatoid arthritis, and psoriasis arthritis	[46–48, 50]
Filgotinib	JAK1	Phase II study in CD	None	[51]
Upadacitinib	JAK1	Phase II studies: successful in UC; primary endpoint failed in CD	For rheumatoid arthritis	[52, 53]
TD-1473	Pan-JAK with only intestinal exposure	Small Ib study in UC	None	[54]
BMS-986165	TYK2	No data in IBD yet	None	[52]
Brepocitinib (PF-06700841)	TYK2 and JAK1	No data in IBD yet	None	[52]
PF-06651600	JAK3	No data in IBD yet	None	[52]

. Ann Rheum Dis. 2018 Feb;77(2):175-187.

Emerging Treatment Options in Inflammatory Bowel Disease: Janus Kinases, Stem Cells, and More. Digestion. 2020;101 Suppl 1:69-82.

Tofacitinib στην Ελκώδη Κολίτιδα

Tofacitinib in Ulcerative Colitis: Real-world Evidence From the ENEIDA Registry

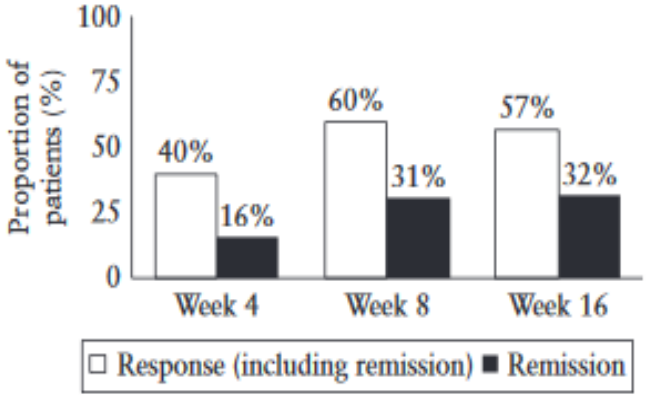


Figure 2. Short-term effectiveness of tofacitinib in ulcerative colitis [last-observation-carried-forward method].

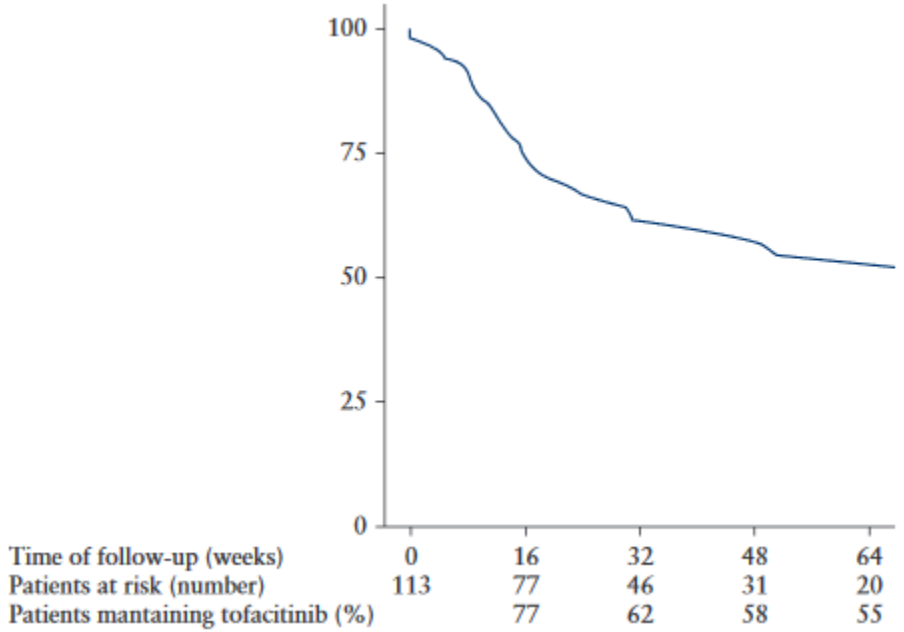


Figure 3. Survival curve of patients maintaining tofacitinib treatment over time.

Καλή αποτελεσματικότητα και δεδομένα ασφάλειας,
Κύρια αιτία διακοπής : primary failure

Real-world Evidence From the ENEIDA Registry. J Crohns Colitis. 2020 Sep 24:jjaa145.

Tofacitinib : η Ρευματολογία συναντά την Γαστρεντερολογία

PA,ΨA
10mg/ημερησίως
προφίλ ασφάλειας

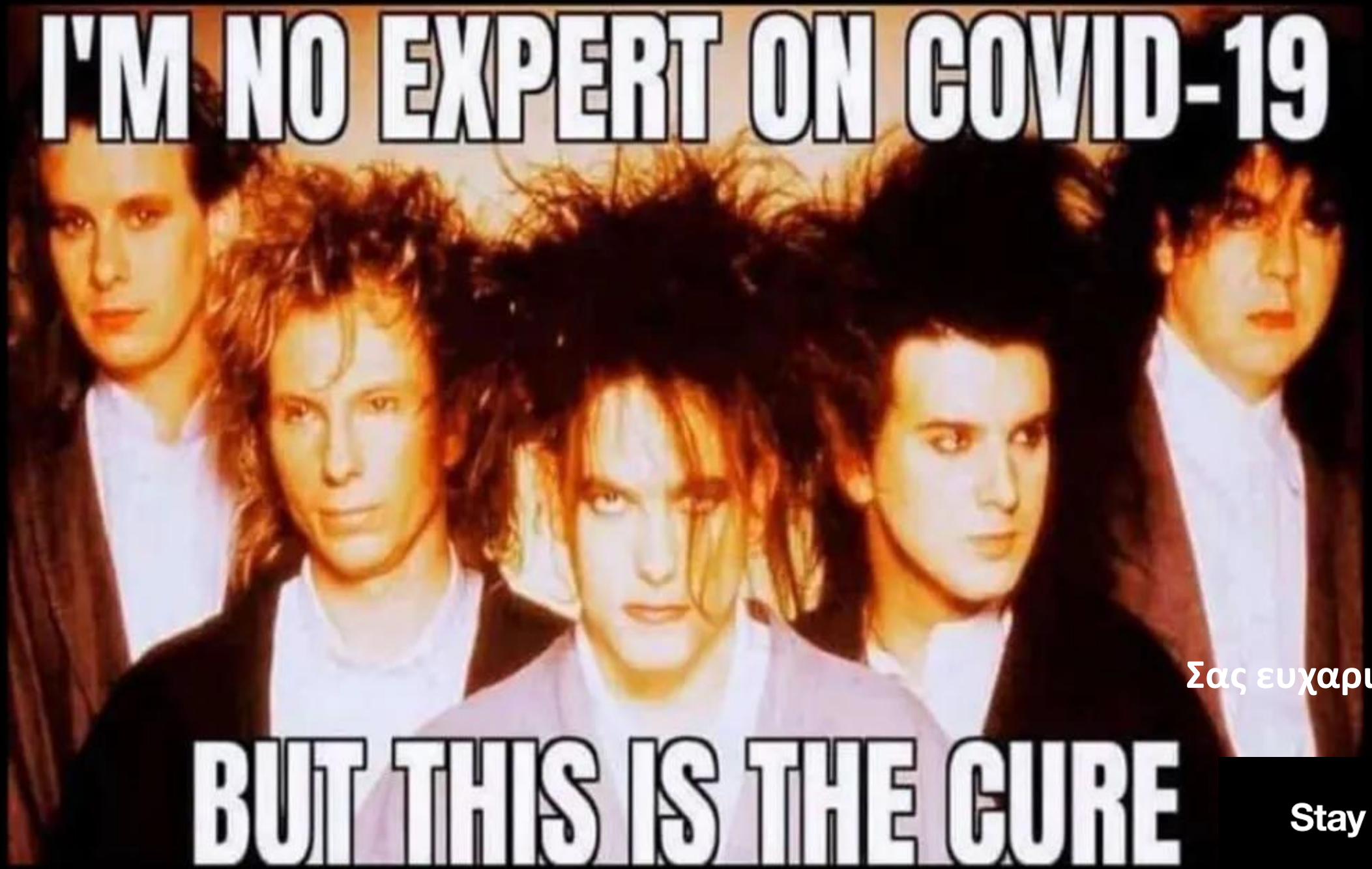
Tofacitinib

Ελκώδης κολίτιδα
20mg/ημερησίως
προφίλ ασφάλειας

↑Ανεπιθύμητες ενέργειες

Take home notes

- **Από όλα τα csDmards η Μεθοτρεξάτη(sc≥15mg) καλύπτει καλύτερα το φάσμα μίας εντεροπαθητικής αρθρίτιδας**
- **Δύναται η βραχυπρόθεσμη λήψη ΜΣΑΦ ειδικά σε Ελκώδη Κολίτιδα (προτιμώνται τα νεότερα σκευάσματα)**
- **Ως Tnf(i) επιλογή σε ασθενείς με ΙΦΝΕ να αποφεύγεται η Ετανερσέπτη**
- **Σε διαγνωσμένη ΙΦΝΕ να μην χορηγείται το Secukinumab και επί υψηλής υποψίας για ΙΦΝΕ ,παραπομπή σε ειδικό**
- **Το tofacitinib αποτελεί μια καλή επιλογή σε εντεροπαθητική ελκώδη κολίτιδα (όχι νόσο Crohn)**
- **Σε συνύπαρξη «αρθρίτιδας» με ΙΦΝΕ πάντα παραπομπή και συνεργασία με Γαστρεντερολόγο**



Σας ευχαριστώ !!

Stay safe